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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/094,921	06/15/98	LINDHOFER	H 80309

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EXAMINER	
HOLLERAN, A	
ART UNIT	**PAPER NUMBER**
1642	9
DATE MAILED:	05/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/094,921	Lindhofer t al
Examiner	**Group Art Unit**
Anne Holleran	1642

☒ Responsive to communication(s) filed on *Mar 13, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-26* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-26* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Applicati n Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachm nt(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of a single disclosed species of antibodies that bind T cells via CD3 and the bi/tri specific antibody combination rat/mouse, in Paper No. 8, filed March 13, 2000, is acknowledged.

Claims 1-26 are pending.

Claims 1-26 are examined on the merits.

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Drawings

3. The drawings are objected to for the reasons indicated on the enclosed PTO-948. Correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it is drawn to a method for ex vivo immunization of humans and animals with method steps that appear to be the steps of a method of making a vaccine preparation.

Claim 1 is further vague and indefinite because it is not clear if in step "c" the tumor cells may be incubated with more than one antibody. If Applicant intends only one antibody then amendment of the recitation "and/or" to read "or" is required.

Claim 3 is vague and indefinite because the list of cells to which the antibodies may bind should be recited in the alternative. For examination purposes, the antibodies referred to in claim 3 are considered to be capable of binding to monocytes, macrophages, dendritic cells, natural kill cells or activated neutrophils.

Claim 3 is further vague and indefinite because it is not clear if only the activated neutrophils are limited to Fcγ receptor I-positive neutrophils or if all of the cell types are Fcγ receptor I-positive.

Claim 5 is vague and indefinite because the list of T cell receptor types should be listed in the alternative.

Claim 8 is vague and indefinite because the specificities of the recited bispecific antibodies should be listed in the alternative.

Claim 9 is vague and indefinite because of improper Markush language, i.e. "selected from one or more of the following isotype combinations:". Applicant is advised to amend the claim to recite "selected from the group consisting of".

Claim 10 is vague and indefinite in the recitation "said bispecific antibody is selected from a heterologous rat/mouse bispecific antibody". It is not clear if Applicant intends the antibody to be selected from the group of rat/mouse bispecific antibodies listed in claim 9 or if Applicant intends that "said bispecific antibody is a heterologous rat/mouse bispecific antibody".

Claim 11 is vague and indefinite because it does not further limit the method of claim 1. The recited characteristics of the trispecific antibody of claim 11 are recited in claim 1.

Claim 12 is vague and indefinite because the species of trispecific antibody are not listed in the alternative.

Claim 13 is vague and indefinite because it is not clear if the recitation "(short-term incubation)" is intended as a method step. Also, it is not clear what the antibody-tumor cell preparation is incubated with.

Claim 13 is further vague and indefinite because the recitation "the tumour cells charged with antibodies" lacks antecedent basis. For examination purposes the recitation is considered to mean an antibody-tumor cell preparation or composition.

Claims 13 and 14 are vague and indefinite because each claim appears to add a limitation to the method of claim 1 by the addition of a new step. Thus, claims 13 and 14 should indicate that a "step d" is to be added.

Claim 14 is vague and indefinite because it is not clear if the recitation "(long-term incubation)" is intended as a method step.

Claim 14 is further vague and indefinite because it is not clear what the components of the resulting vaccine composition are. It is not clear if the method produces a vaccine composition that has the same as the composition of claim 1, if the method produces a vaccine composition that further comprises peripheral blood mononuclear cells or if the method produces a vaccine composition consisting of activated peripheral blood mononuclear cells.

Claim 19 is vague and indefinite in the recitation "said tumour cells are added". It is not clear to what the tumor cells are added because there is not addition step in claim 1, from which claim 19 depends.

Claims 20 and 22 are vague and indefinite because the bispecific and trispecific antibodies should be listed in the alternative.

Claims 23 and 24 provides for the use of tumor cell containing preparations, but because the claim does not set forth any steps involved in the method, it is unclear what method applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 25 is vague and indefinite because it does not appear to be limit the method of claim 1 from which it depends.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 23 and 24 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Specification

6. The specification is objected to because it relies on a reference to subject matter disclosed within a claim. Specifically, page 3, lines 8-11. Amendment of the specification to delete lines 8-11 is required.

Notes

7. Applicant's attention is drawn to term "Biespiel 2" on page 29. An amendment to change this to "Example 2" is suggested.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 23 and 24 are drawn to method of prevention of tumorous diseases as well as to methods of treatment. Thus, claims 23 and 24 can be interpreted as drawn to methods for the prevention of cancer. Because the method requires the use of bispecific or trispecific antibodies which are specific for tumor antigens, and because a method of prevention implies that the cancer has not occurred yet, it is not possible to understand how Applicant will know which antibodies to use. Thus, the specification provides no teachings that would allow one of skill in the art to understand that Applicant was in possession of a method for the prevention of cancer.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 14, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Honsik et al (U.S. Patent 4,844,893; published July 4, 1989).

Claims 14, 17 and 18 may be interpreted to be drawn to methods of making a vaccine preparation that comprises activated peripheral blood mononcuclear cells. As indicated above claim 14 (and dependent claims 17 and 18) is vague and indefinite.

Honsik et al teach a method of using bispecific antibodies for the preparation of ADCC competent peripheral blood mononuclear cells comprising incubating peripheral blood mononuclear cells with bispecific antibodies which bind to the Fc receptor, to a tumor cell antigen and also bind to T-cells. The peripheral blood mononuclear cells are then mixed with tumor cells. Thus, Honsik et al teach a method of making a cellular vaccine against cancer cells that is the same as that of claims 14, 17 and 18.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1- 8, 11-13, 15, 16 and 19-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Volker et al (U.S. Patent 5,911,987; published 5,911,987; 102(e) date Feb. 21, 1997) in view of Deo et al (U.S. Patent 5,837,243; published Nov. 17, 1998; files June 7, 1996).

Claim 1 is interpreted to be drawn to a method of making a vaccine composition comprising isolated autologous tumor cells, treating the tumor cells to prevent survival and incubating the treated tumor cells with bispecific or trispecific antibodies which bind to a T cell, bind to at least one antigen on a tumor cell and bind to the Fc receptor of Fc receptor-positive cells. Claim 2 specifies the Fc receptor as the Fcγ receptor, I, II or III. Claim 3 specifies that the antibodies bind to monocytes, macrophages, dendritic cells, natural killer cell or activated neutrophils by the Fcγ receptor I. Claim 4 specifies that the antibodies are capable of inducing tumor-reactive complement-binding antibodies. Claim 5 adds that limitation that antibodies be specific for CD3. Claim 6 adds the limitation that the antibodies elicit the CD40, CD80, CD86, ICAM-1 or LFA-3 antigens or the secretion of cytokines by Fc-receptor positive cells. Claim 7 adds the limitation that the cytokines secreted be IL-1, IL-2, IL-4, IL-6, IL-8, IL-12 or TNFα. Claim 8 adds the limitation that the bispecific antibody contains an anti-CD3 and an anti-tumor-associated antigen specificity. Claim 11 appears to have the same scope as that of claim 1. Claim 12 adds the limitation that the trispecific antibody contains an anti-CD3 and an anti-tumor-associated antigen specificity. Claim 13 adds a further step to the method, that of a short-term incubation step. Claims 15 and 16 specify the duration of the incubation period. Claim 19 adds the limitation that the amount of tumor cells used in the method is 10^7 to 10^9 cells. Claim 20

adds the limitation that the bispecific or trispecific antibodies be added in an amount of 2-100 ug. Claim 21 specifies that the cell treatment procedure is limited to irradiation. Claim 22 adds the limitation that the bispecific or trispecific antibodies are capable of activating the Fc receptor positive cells. Claim 25 appears to be of the same scope as that of claim 1.

Claims 23 and 24 are interpreted to be drawn to method of treatment of cancer comprising injecting the vaccine preparations of claim 1. Claim 26 is drawn to a pharmaceutical composition that is prepared by the method of claim 1.

Volker et al teaches a method of preparing a cellular vaccine from autologous tumor cells by isolating the tumor cells, freezing and thawing the isolated tumor cells (assumed to inactivate the tumor cells), infecting the tumor cells with Newcastle Disease Virus to antigenize the tumor cells and incubating the tumor cells with a bispecific cell bonding reagent which has a specificity for a Newcastle Disease Virus antigen and has a specificity for a T-cell (column 6, lines 58 - column 8, lines 13). The amount of tumor cells used to prepare the vaccine is 10^7 cells. The incubation step with the bispecific cell bonding reagent lasts for 30 minutes. The cells may be treated with 200 Gy radiation. The bispecific cell bonding reagent may have specificity for CD3. The cell bonding reagents may be made up of antibodies or fragments of antibodies. Volker et al also include a step of injecting the cellular vaccine preparation intradermally using a 0.9x40ml cannula.

Volker et al does not teach a bispecific or trispecific antibody (or cell bonding reagent) that has a specificity for a Fc receptor. However, the usefulness of using bispecific antibodies

comprising an anti-Fc receptor specificity in the treatment of cancer is well known in the art as taught by Deo et al (see column 11, lines 11-16). Deo et al also teaches that the Fc receptor-specific antibodies are useful for binding to Fc receptor bearing cells such as monocytes, macrophages, neutrophils and dendritic cells which are cells that are involved in specific killing of target cells and presenting antigens to the immune system (column 6, lines 13-18). Deo et al also teaches that the Fc receptor-specific antibodies are useful for presenting antigen to antigen presenting cells of a patient (column 9, lines 20-30). Deo et al disclose a specific embodiment of a bispecific antibody, H22, which contains an anti-FcγI receptor (FcγRI, see column 17, lines 60-67) and which possess ADCC activity mediated through FcγRI binding . Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the cell vaccine preparation method of Volker et al to include a cell bonding reagent that had an Fc receptor specific region, either in the form of an Fc receptor portion of an antibody or a region that would be specific for an Fc receptor. One of ordinary skill in the art would have been motivated to alter the vaccine preparation method of Volker et al to include antibodies with an Fc receptor binding specificity because of the teachings of Deo et al concerning the importance of the Fc receptor in the recruitment and stimulation of Fc receptor containing cells which would result in improved antigen presentation to the immune system.

Conclusion

No claim is allowed. Claims 9 and 10 are free of the art.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

ALH

Anne L. Holleran
Patent Examiner
May 21, 2000

Yvonne Eyler

YVONNE EYLER, PH.D
PRIMARY EXAMINER